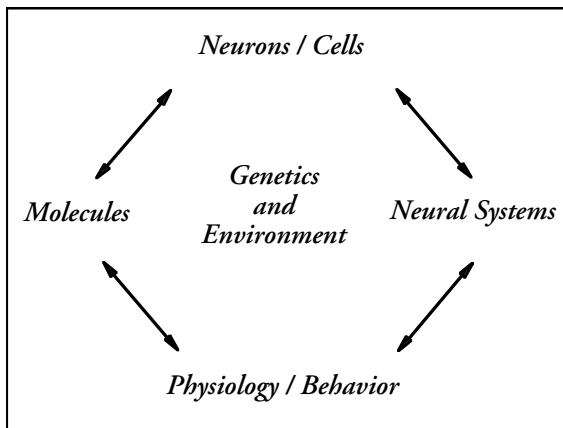


# Neurobiology of Addiction

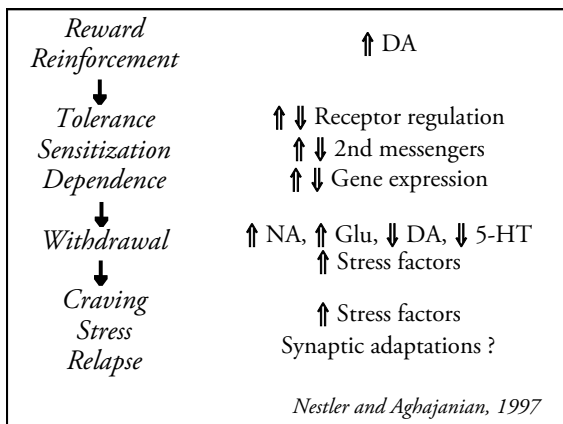
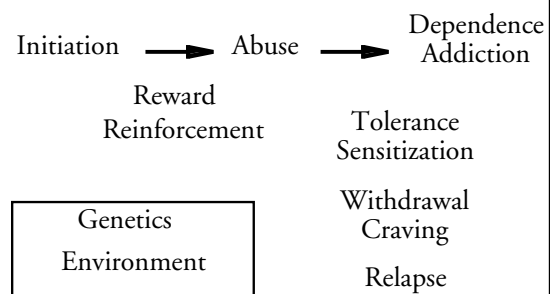
Dr. Leo Kadehjian  
Palo Alto, California

## Mother Nature vs. Chemists

<u>Stimulants</u>		<u>Sedatives</u>	
Caffeine	Amphetamines	Ethanol	Barbiturates
Nicotine	MDMA		Benzodiazepines
Cocaine			Methaqualone
Ephedrine			
Khat			
<u>Opiates</u>		<u>Hallucinogens</u>	
Morphine	(Heroin)	Mescaline	(LSD)
Codeine	(Oxy-, Hydro-)	Psilocybin	PCP
	Methadone, LAAM	Marijuana	
	Fentanyl		
	Meperidine		



## Terminology



Nestler and Aghajanian, 1997

## Drug Dependence, A Chronic Medical Illness

	<u>Heritability</u>	<u>Treatment Compliance</u>	<u>Relapse Rates</u>
Diabetes	.8 Type II .3-.55 Type I	<60% Type I	30-50% Type I
Hypertension	.25-.5	<40%	50-70%
Asthma	.36-.7	<40%	50-70%
Drug Abuse	.61 nicotine (m,f) .55 alcohol (m) .52 marijuana (f) .34 heroin (m)	40-60%	40-60%

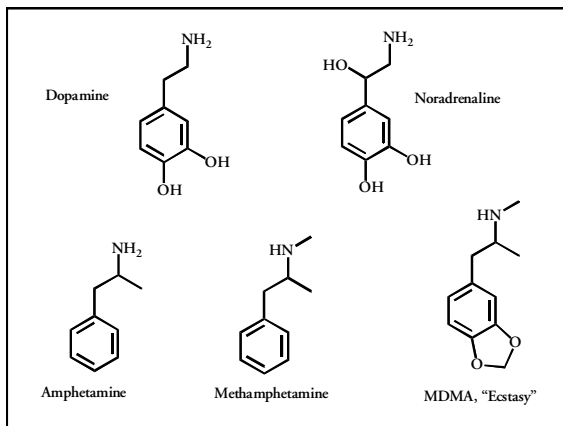
A. McLellan et al., 2000

## Neurotransmitters

<i>100,000</i>	:	<i>1,000</i>	:	<i>1</i>
Amino acids		Monoamines		Peptides
Glutamate		Noradrenaline		Enkephalins
Aspartate		Adrenaline		Substance P
GABA		Dopamine		Insulin
Glycine		Serotonin		Vasopressin
		Histamine		Oxytocin
		Acetylcholine		Many others

## Dopamine

- ▶ Parkinson's disease (deficit)
- ▶ Schizophrenia (excess)
- ▶ Role in reward circuits (1954)
  - Nicotine, alcohol, marijuana
  - cocaine, morphine, amphetamines



## Dopamine and Behavioral Control

*"In addition, dopamine effects in the PFC may impair the ability of the addicted person to suppress prepotent drug-seeking behavior."*

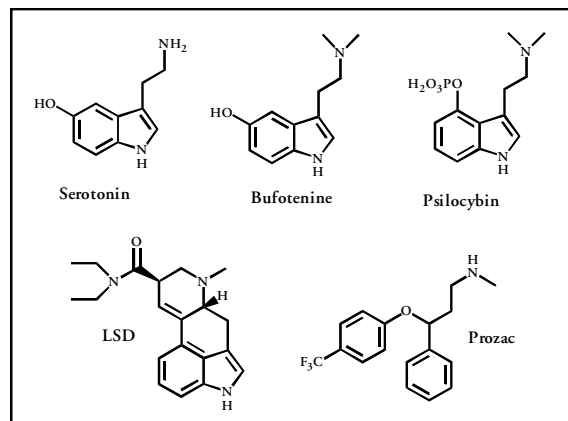
*"Because these drugs directly engage dopamine-mediated reinforcement learning signals, they generate a feedback loop that reinforces behavior leading to drug consumption, establishing a vicious cycle of action and learning that explains the compulsive nature of drug addiction."*

*"In this framework, the addicted person's PFC can no longer even categorize decision problems correctly, much less regain control over the choices that their nervous systems deem valuable."*

*P. Read Montague et al., 2004*

## Serotonin

- ▶ Generally inhibitory
- ▶ Site of action for LSD, hallucinogens
- ▶ Role in aggression, violence, suicide, depression, alcoholism, cocaine use
- ▶ Neurons damaged by MDMA, fenfluramine



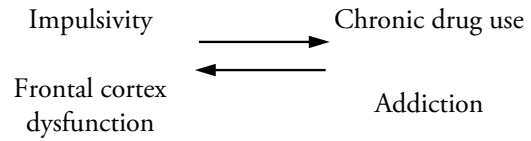
### Addiction:

- Compulsion to seek drug
- Loss of control
- Negative emotional state, withdrawal

### 3 Stages:

- Binge, intoxication      Ventral tegmentum, ventral striatum
- Negative affect, withdrawal      Extended amygdala
- Preoccupation, craving
  - Craving      OFC, PFC, dorsal striatum, basolateral amygdala, hippocampus, insula
  - Poor inhibitory control      Cingulate gyrus, DLPFC, inferior FC

*G. Koob and N. Volkow, 2010*



### Impulsivity → Compulsivity

Positive reinforcement  
drives behavior

Negative reinforcement  
drives behavior

Unplanned reactions  
without regard to  
negative consequences

Continued use despite  
adverse consequences

### Prefrontal Cortex Circuits in Addiction

Impaired inhibition control, impaired decisionmaking

- Dorsolateral prefrontal cortex  
Goal identification, selection, reward processing, guiding behaviors
- Orbitofrontal cortex  
Decisionmaking, impulsivity, behavioral disinhibition, drug seeking despite adverse consequences, compulsive repetitive behaviors
- Anterior cingulate cortex  
Assessment of consequences, error and conflict detection

*J. Feil et al., 2010*

### Variation in motivational control over reward cues

"Therefore, it is possible to predict, *before any drug experience*, which rats will find drug cues more desirable, will exhibit greater motivation to take drugs, and will be more likely to relapse."

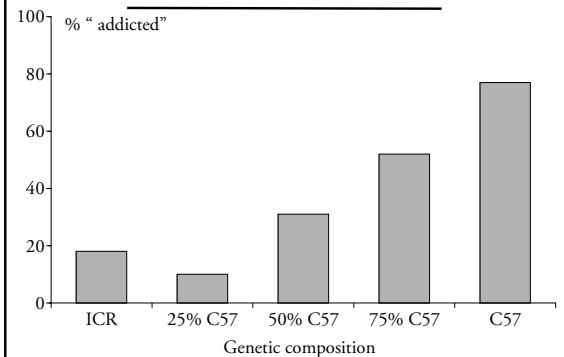
- Neurobiological differences, DA
- Heritable
- Influenced by early life experiences

Susceptibility to impulse-control disorders:

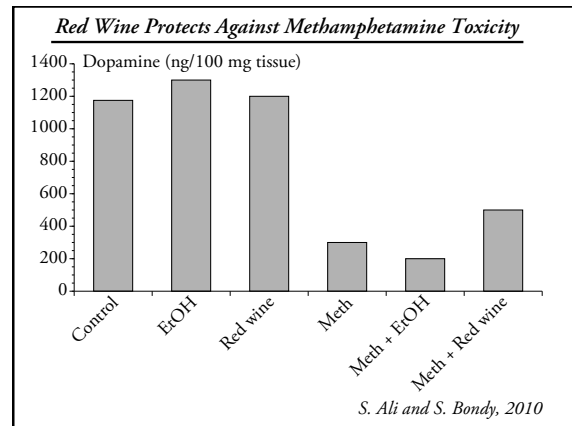
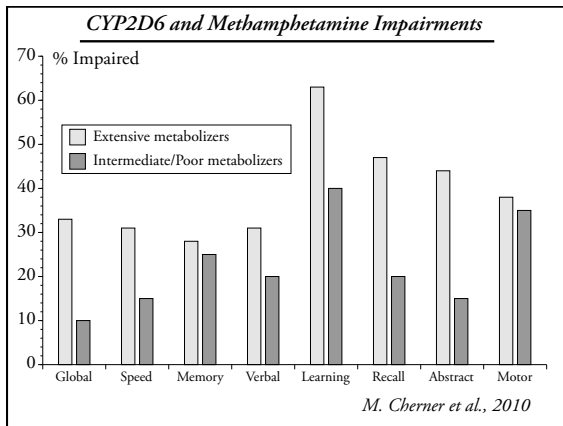
- Genetic
- Epigenetic
- Environmental
- Neural systems

*B. Saunders et al., 2013*

### Genetics / Cocaine Addiction



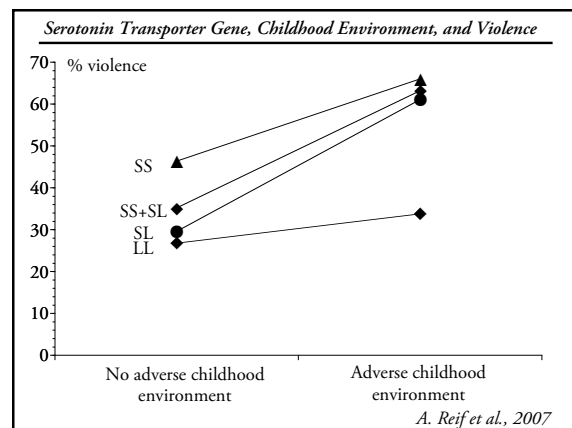
*E. Ruiz-Durántez et al., 2006*



**Serotonin, Genes, Adverse Childhood Environment, and Violence**

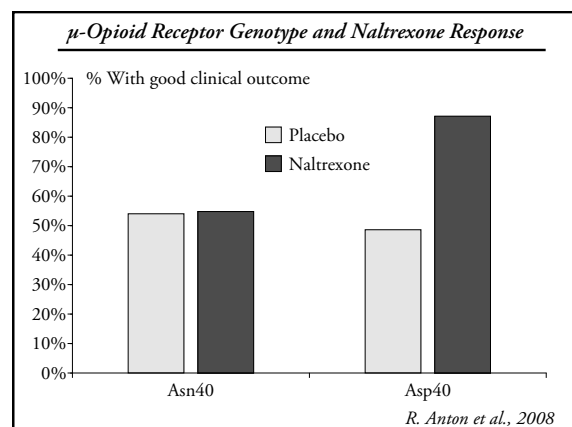
	Odds ratio for violence
Adverse childhood environment	4.1 (2.6–6.5)
MAO-A short vs. long alleles	2.3 (1.1–4.7)
5HTTLPR * adverse childhood environment	0.2 (0.1–0.4)
No vs. history of substance abuse	0.5 (0.2–1.0)
No vs. history of personality disorder	0.9 (0.4–1.9)

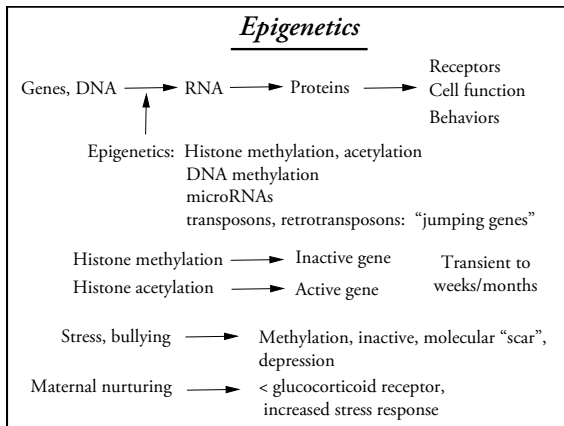
*A. Reif et al., 2007*



**Treatment**

<u>Antagonists</u>	<u>Agonists</u>
Disulfiram	Methadone, LAAM
Naloxone	Buprenorphine
	GHB ?
Antibodies ?	
Vaccines ?	<u>Anti-craving</u>
Enzymes ?	Naltrexone
	Acamprosate
	$\gamma$ -vinyl-GABA ?





***Does neuroscience undermine the role of personal responsibility for development of and recovery from addiction?***

Examined effect of exposure to neuroscience on counselor views

n = 231 NAADAC counselors from 44 states

For those with more exposure to neuroscience:

- ▶ Development: Biofactors even more influential
- ▶ Recovery: Personal responsibility even more influential (!?)

*T. Steenbergh et al., 2012*